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EXPERIMENTAL STUDIES

Dual Natriuretic Peptide System in Experimental Heart Failure

GORDON W. MOE, MSc, MD, FACC, ETIENNE A. GRIMA, MSc, NORMAN L. M. WONG, PHD,* ROBERT J. HOWARD, MD, FACC, PAUL W. ARMSTRONG, MD, FACC

Toronto, Ontario and Vancouver, British Columbia, Canada

Objectives. **The objectives of this study were 1) to define in an experimental model of heart failure the time course of changes in plasma brain natriuretic peptide concentrations during the development of and recovery from heart failure, and 2) to relate these changes to changes in atrial natriuretic peptide concentration and hemodynamic status.**

Background. **Brain natriuretic peptide is a circulating peptide with homology to atrial natriuretic peptide. However, unlike the latter, its changes during heart failure and its relation to cardiac filling pressures have not been studied.**

Methods. **Eight male mongrel dogs underwent right ventricular pacing at 250 beats/min for 3 weeks until heart failure occurred and were followed up during recovery for 4 weeks after cessation of pacing.**

Results. **Heart failure was characterized by an increase in both left ventricular end-diastolic pressure (6.6 ± 4.1 mm Hg at the control measurements to 35.1 ± 5.9 mm Hg at 3 weeks, $p < 0.01$) and right atrial pressure (6.7 ± 1.1 to 11.4 ± 2.1 mm Hg, $p < 0.01$). Recovery was accompanied by a return of cardiac filling pressures to control level. The time course of change of arterial plasma brain natriuretic peptide concentration was similar to that of atrial natriuretic peptide. Plasma concentrations of both peptides increased after 1 week of pacing (16 ± 4 pg/ml at the control measurement to 59 ± 20 pg/ml at 1 week, $p < 0.001$ for brain natriuretic peptide and 84 ± 55 to 856 ± 295 pg/ml, $p < 0.001$ for atrial natriuretic peptide). The level of both peptides then stayed level with no further increase at 3 weeks and returned to the control value by 4 weeks of recovery. There was an excellent correlation between plasma concentrations of the two peptides ($r = 0.86$, $p < 0.001$) and between the two peptides and cardiac filling pressures. However, compared with atrial natriuretic peptide, plasma brain natriuretic peptide concentration had a smaller percent increase during evolving heart failure and a slower rate of decline at recovery.**

Conclusions. **Brain and atrial natriuretic peptide constitute a dual natriuretic system and are both responsive to changes in cardiac filling pressures in heart failure. However, brain natriuretic peptide appears to be less responsive than atrial natriuretic peptide.**

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Atrial natriuretic peptide was first discovered by De Bold and coworkers (1) as a natriuretic and vasodilator peptide released from the heart in response to volume expansion. Its diverse biologic effects suggest that the peptide is involved in the regulation of blood pressure and volume homeostasis (2,3). Plasma atrial natriuretic peptide concentrations are elevated in patients with heart failure and in association with increased cardiac filling pressures (4–7), indicating that the peptide plays a pathophysiologic role in this condition. Using a canine pacing-induced model of heart failure, we previously demonstrated a progressive increase in plasma norepinephrine concentration and renin activity during evolving heart failure (8) followed by an abrupt decline after cessation of pacing (8,9). By contrast, plasma concentration of atrial natriuretic peptide increased early, reached a plateau as severe heart failure developed and declined more gradually than norepinephrine and renin after cessation of pacing (9).

Brain natriuretic peptide is a 26-amino acid peptide first identified by Sudoh et al. (10) from the porcine brain. This peptide has remarkable homology to atrial natriuretic peptide not only in amino acid sequence but also in its central and peripheral actions (10–14) and its ability to augment cyclic guanosine monophosphate (15,16). It is present not only in the brain but, like atrial natriuretic peptide, is also present in the heart in various species including humans (17–22). Elevated plasma brain natriuretic peptide concentrations have been demonstrated in a small number of patients with conditions of circulatory overload such as chronic renal failure and heart failure (23).

These preliminary data suggest that, like atrial natriuretic peptide, brain natriuretic peptide may also be released from the heart in response to increased atrial pressures in heart failure. Accordingly, the current study was performed to address the following unanswered questions regarding brain natriuretic peptide in heart failure:

1) What is the time course of changes in plasma concentrations of brain natriuretic peptide in the evolution of, and the recovery from, heart failure?

From the Division of Cardiology, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario and the *Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada. This study was supported by grants-in-aid from the Heart and Stroke Foundation of Ontario, Toronto and from the British Columbia Heart Foundation, Vancouver. Dr. Moe is a scholar of the Heart and Stroke Foundation of Ontario.

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Address for correspondence: Gordon W. Moe, MD, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, Canada M5B1W8.

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2) Is there a correlation between plasma brain and atrial natriuretic peptide concentrations?

3) Does plasma brain natriuretic peptide concentration, like atrial natriuretic peptide, bear a relation to cardiac filling pressures?

Methods

Study animals. The study group consisted of eight male mongrel dogs with a mean weight ± SD of 25.2 ± 4.2 kg. All dogs were preconditioned and acclimatized to the laboratory environment at least 1 to 2 weeks before the beginning of the study. The study was approved by the institutional Animal Research Committee.

Induction of heart failure and recovery. The method of inducing heart failure has previously been described in detail (8,9,24,25). In brief, under general anesthesia, a unipolar pacemaker lead was advanced through the external jugular vein into the right ventricular apex, and a programmable pulse generator (Medtronic SX-5985) was inserted into a subcuticular cervical pocket. An arterial cannula for long-term, repeated blood sampling was inserted into the aortic arch through the carotid artery, tunneled underneath the skin and externalized through the dorsal midscapular surface. The animals then recovered from the effects of general anesthesia for ≥1 week before control study measurements were made. These and all subsequent studies were performed with the dog in the conscious state. All dogs underwent a control clinical, radiographic, echocardiographic and hemodynamic assessment.

After the control study measurements and blood sampling, continuous right ventricular pacing (250 beats/min) was initiated and maintained for 3 weeks. During this period, the dogs underwent weekly clinical, radiographic and echocardiographic examinations to monitor the development of heart failure. The techniques for radiographic and echocardiographic examinations have also been described in detail (24,25). Blood samples were obtained weekly from the long-term aortic cannula for measurements of arterial atrial and brain natriuretic peptide concentration, norepinephrine concentration and plasma renin activity. After 3 weeks of pacing, all eight animals developed heart failure, and a repeat hemodynamic assessment was obtained. Thereafter, the pacemaker was reprogrammed to allow resumption of normal sinus rhythm and recovery from heart failure. Clinical, radiographic and echocardiographic assessments together with arterial blood sampling were continued for an additional 4 weeks (recovery phase), after which time the final hemodynamic study was performed.

Hemodynamic assessments. In the conscious state, all dogs underwent hemodynamic assessments during sinus rhythm in the control period, after 3 weeks of pacing (heart failure) and at 4 weeks after cessation of pacing (recovery). Under lidocaine local anesthesia, right-sided pressures were obtained using a thermodilution Swan-Ganz catheter introduced through the femoral vein. Left ventricular and aortic pressures were obtained by a double-transducer micromanometer-tipped catheter (Millar MIKRO-TIP) introduced through the femoral artery.

Plasma atrial and brain natriuretic peptide and other neurohormonal measurements. Arterial blood samples for the measurement of plasma concentrations of atrial and brain natriuretic peptide, norepinephrine and renin were obtained 1) at the time of the control study; 2) at 1, 2 and 3 weeks after the initiation of pacing; and 3) at 48 h and 4 weeks after the cessation of pacing. Plasma norepinephrine concentration was determined using high pressure liquid chromatography (8); plasma renin activity was determined using radioimmunoassay (23). Plasma atrial natriuretic peptide concentration was determined by radioimmunoassay with a commercially available antibody kit (Peninsula Laboratories), as previously described (26–28). Plasma brain natriuretic peptide concentration was also determined by radioimmunoassay. Brain natriuretic peptide antibody was prepared with pBNP-26 commercially available from Peninsula Laboratories. This antibody cross-reacts well with canine brain natriuretic peptide but does not cross-react with atrial natriuretic peptide, rat or human brain natriuretic peptide. Brain natriuretic peptide was labeled with iodine-125 (^{125}I) by the chloramine-T method. pBNP-26 was used to construct the standard curve (2 to 500 pg/tube). The radioimmunoassay was done using a method previously described for atrial natriuretic peptide (26,27). About 15,000 cpm of ^{125}I-labeled brain natriuretic peptide was added after a 24-h preincubation period and was incubated again overnight at 4°C. Free and bound fractions were separated by goat-rabbit gamma globulin (100 μl, 1:50) in the presence of normal rabbit serum (100 μl 1%).

Statistical analysis. Changes of all study variables over time were each assessed by analysis of variance followed by the Dunnett test. Comparison of percent change of the two peptides was made by two-way analysis of variance followed by the Dunnett test. Assessment of the relations between hemodynamic variables and the two peptides was made by linear regression analysis using dummy variables to account for between-animal variability. The data are presented as mean value ± SD. A probability value < 0.05 was considered significant.

Results

After 3 weeks of continuous rapid right ventricular pacing, all dogs developed heart failure, as evidenced by the appearance of apathy; ascites; radiographic evidence of cardiomegaly; pleural effusions, and pulmonary edema. Echocardiographically derived left ventricular ejection fraction decreased from 53.0 ± 7.9% at control measurements to 28.7 ± 7.4% at 1 week and further to 20.1 ± 6.1% at 3 weeks of pacing (both $p < 0.001$). At 4 weeks after cessation of pacing, the aforementioned clinical and radiographic signs of circulatory congestion were no longer present. Ejection fraction increased to 37.5 ± 6.7% by 48 h and to 40.2 ± 7.6% by 4 weeks of recovery,

Table 1. Hemodynamic Variables in Eight Dogs

	Heart Rate (beats/min)	MAP (mm Hg)	RAP (mm Hg)	LVEDP (mm Hg)	PCWP (mm Hg)	Cardiac Output (liters/min)
Control	87 ± 23	114 ± 21	6.7 ± 1.1	6.6 ± 4.1	10.0 ± 1.8	4.5 ± 1.4
3 wk	147 ± 42*	110 ± 13	11.4 ± 2.1*	35.1 ± 5.9*	27.2 ± 6.9*	2.6 ± 0.4†
4wkR	75 ± 29	108 ± 21	7.3 ± 3.5	7.8 ± 4.3	10.6 ± 2.1	3.8 ± 1.3

*$p < 0.01$, †$p < 0.05$ versus control value. Data are expressed as mean value ± SD. All values were acquired during sinus rhythm. 4wkR = recovery (4 weeks after cessation of pacing); LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; 3 wk = 3 weeks of pacing (severe heart failure).

although it was still significantly lower than control values ($p < 0.01$ and $p < 0.05$ respectively).

Hemodynamics (Table 1). Intrinsic heart rate, left ventricular end-diastolic pressure, pulmonary capillary wedge pressure and right atrial pressure all increased markedly after 3 weeks of pacing, whereas mean arterial pressure remained unchanged and cardiac output decreased. At 4 weeks after cessation of pacing, heart rate, cardiac filling pressures and cardiac output all returned to control values.

Plasma norepinephrine concentration and renin activity (Table 2). Plasma norepinephrine increased significantly after 1 week of pacing and continued to increase at the time of severe heart failure. After cessation of pacing, norepinephrine declined rapidly to control value by 48 h of recovery. In contrast to plasma norepinephrine, plasma renin activity was not significantly changed either during chronic pacing or at recovery.

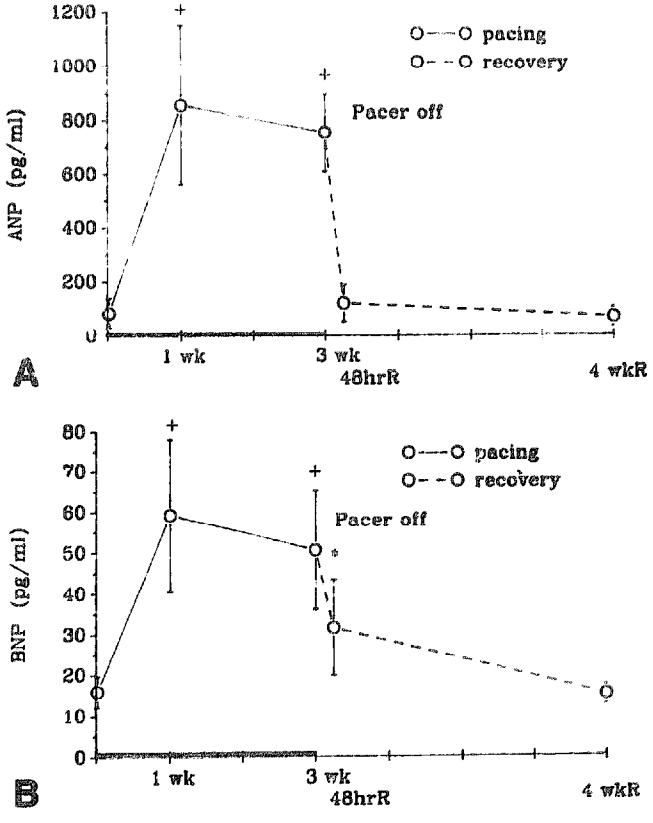
Plasma atrial and brain natriuretic peptide concentrations (Fig. 1 and 2). The changes in arterial plasma concentrations of atrial and brain natriuretic peptide during the development of and recovery from heart failure are shown in the upper and lower panels of Figure 1. To provide a direct comparison of the two natriuretic peptides, the changes are also expressed as percent change from the control values for both peptides and are shown in Figure 2. In general, the time course of the changes of the two peptides were similar; that is, plasma concentrations of both peptides peaked at 1 week of pacing (atrial and brain natriuretic peptide, 84 ± 55 and 16 ± 4 pg/ml at control to 856 ± 295 and 59 ± 20 pg/ml, respectively, both $p < 0.001$) and then returned toward control values by 4 weeks of recovery. However, the percent increases in brain natriuretic peptide at 1 week and 3 weeks of pacing were significantly less than those of atrial natriuretic peptide (Fig. 2). Furthermore, plasma brain natriuretic peptide concentration was still significantly increased from control values at 48 h after cessation of pacing, whereas plasma atrial natriuretic peptide concentration had already returned to control level (Fig. 1). Indeed, when expressed as percent change from the 3-week pacing value, the decrease (36 ± 24%) in plasma brain natriuretic peptide at 48 h of recovery was significantly smaller than that (83 ± 8%, $p < 0.05$) of atrial natriuretic peptide.

Table 2. Plasma Norepinephrine and Renin in Eight Dogs

	Norepinephrine (pg/ml)	Renin (ng/ml per/h)
Control	195.8 ± 44.7	1.4 ± 1.1
1 wk	542.8 ± 172.0*	1.5 ± 1.1
3 wk	834.8 ± 416.1†	2.1 ± 2.2
48hrR	268.4 ± 66.4	0.8 ± 0.2
4wkR	193.8 ± 65.8	1.1 ± 0.7

*$p < 0.01$, †$p < 0.001$ versus control value. Data are expressed as mean value ± SD. 48hrR and 4wkR = 48 h and 4 weeks, respectively, after cessation of pacing (recovery); 1 wk = 1 week of pacing; 3 wk = 3 weeks of pacing (severe heart failure).

Figure 1. Changes in plasma concentrations of (A) atrial natriuretic peptide (ANP), and (B) brain natriuretic peptide (BNP) at control measurement and at 1 and 3 weeks of pacing (1 wk, 3 wk, solid lines) and at 48 h and 4 weeks of recovery after cessation of pacing (48hrR, 4 wkR, dashed lines). *$p < 0.05$, †$p < 0.001$ versus control.



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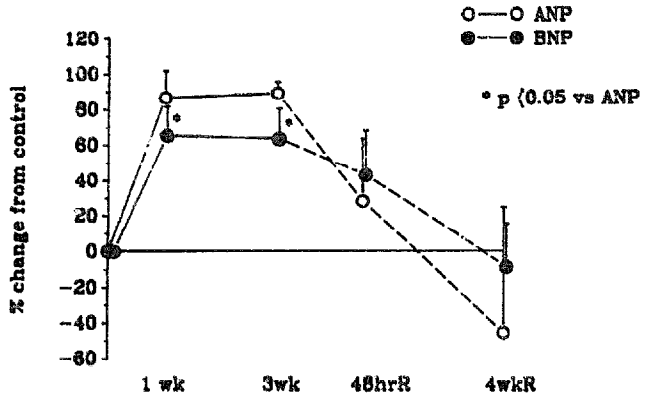
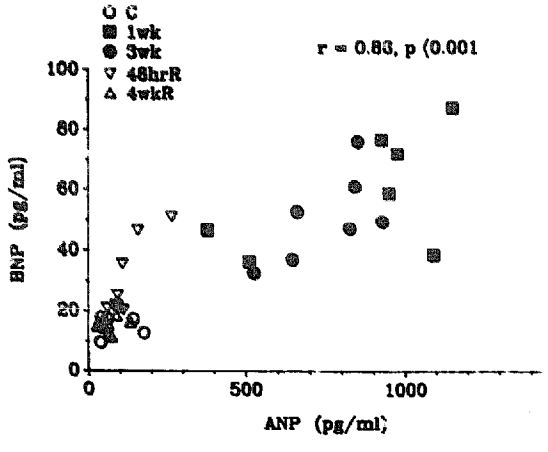


Figure 2. Percent change from control level of plasma concentrations of atrial natriuretic peptide (ANP, open circles) and brain natriuretic peptide (BNP, solid circles) at 1 and 3 weeks of pacing (1 wk, 3 wk, solid lines) and 48 h and 4 weeks of recovery after cessation of pacing (48hrR, 4wkR, dashed lines).

Relation between plasma atrial and brain natriuretic peptide concentrations (Fig. 3). To determine whether there is a relation between plasma concentrations of the two peptides, plasma brain natriuretic peptide concentrations were correlated with those of atrial natriuretic peptide. The data incorporating all study time points are shown in Figure 3. As can be seen, there was a strong correlation between plasma atrial and brain natriuretic peptide concentrations over a wide range of time points and plasma concentrations ($r = 0.86$, $p < 0.001$).

Relations between plasma concentrations of natriuretic peptides and cardiac filling pressures (Fig. 4). To assess whether the release of these peptides was related to an increase in cardiac filling pressures, plasma concentrations of the two peptides were plotted against the corresponding left ventricular end-diastolic pressure and right atrial pressures. This was performed over a broad range of peptide concentrations and cardiac filling pressures using all study time points at which hemodynamic studies were conducted (that is, at control measurement, at 3 weeks of pacing and at 4 weeks of recovery; Fig. 4). Figure 4A shows that atrial natriuretic peptide concentration increased markedly at 3 weeks, in parallel with increased left ventricular end-diastolic pressure, and declined to control values at 4 weeks of recovery, again in parallel with the decrease in left ventricular end-diastolic pressure. Analyzing all study time point, atrial natriuretic peptide concentration correlated well with left ventricular end-diastolic pressure ($r = 0.93$, $p < 0.001$). It also correlated with pulmonary capillary wedge pressure ($r = 0.94$, $p < 0.001$, not shown in Fig. 4) and modestly with right atrial pressure ($r = 0.74$, $p = 0.002$, Fig. 4B). Brain natriuretic peptide concentration also correlated well with left ventricular end-diastolic pressure ($r = 0.91$, $p < 0.001$, Fig. 4C), pulmonary capillary wedge pressure ($r = 0.87$, $p < 0.001$, not shown) and right atrial pressure ($r = 0.84$ $p < 0.001$, Fig. 4D).

Figure 3. Relation between plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) at control measurement and at 1 and 3 weeks of pacing (C, 1wk, 3wk) and 48 h and 4 weeks of recovery after cessation of pacing (48hrR, 4wkR).



Discussion

Our current study contains three new observations regarding brain natriuretic peptide in the model of pacing-induced heart failure. 1) The time course of changes in brain natriuretic peptide in general parallels that of atrial natriuretic peptide, with an early increase followed by a plateau during evolving heart failure and a decrease during recovery from heart failure.

2) There is a close correlation between plasma atrial and brain natriuretic peptide concentration. However, the percent increase during evolving heart failure is smaller (Fig. 2) and the rate of decline during recovery from heart failure is slower (Fig. 1 and 2) with brain natriuretic peptide.

3) Finally, both atrial and brain natriuretic peptide concentrations bear close relations to cardiac filling pressures.

Hemodynamic variables, plasma norepinephrine and renin activity. The hemodynamic characterization of heart failure after 3 weeks of pacing includes an increase in intrinsic heart rate, left- and right-sided cardiac filling pressures and a decrease in cardiac output. All variables returned to control values at 4 weeks after cessation of pacing. These findings are consistent with those reported in our previous studies (24,25). Although we did not perform hemodynamic studies 48 h after cessation of pacing in the current study, we previously showed (24) that cardiac filling pressures approximate control values by 48 h after cessation of pacing.

The changes in plasma norepinephrine concentrations are also consistent with our previous observations (8), demonstrating a progressive increase in plasma concentrations during the 3 weeks of pacing and a very rapid decline after cessation of pacing. In the present study there was no significant increase in plasma renin activity after 3 weeks of pacing. This finding is consistent with our previous observa-

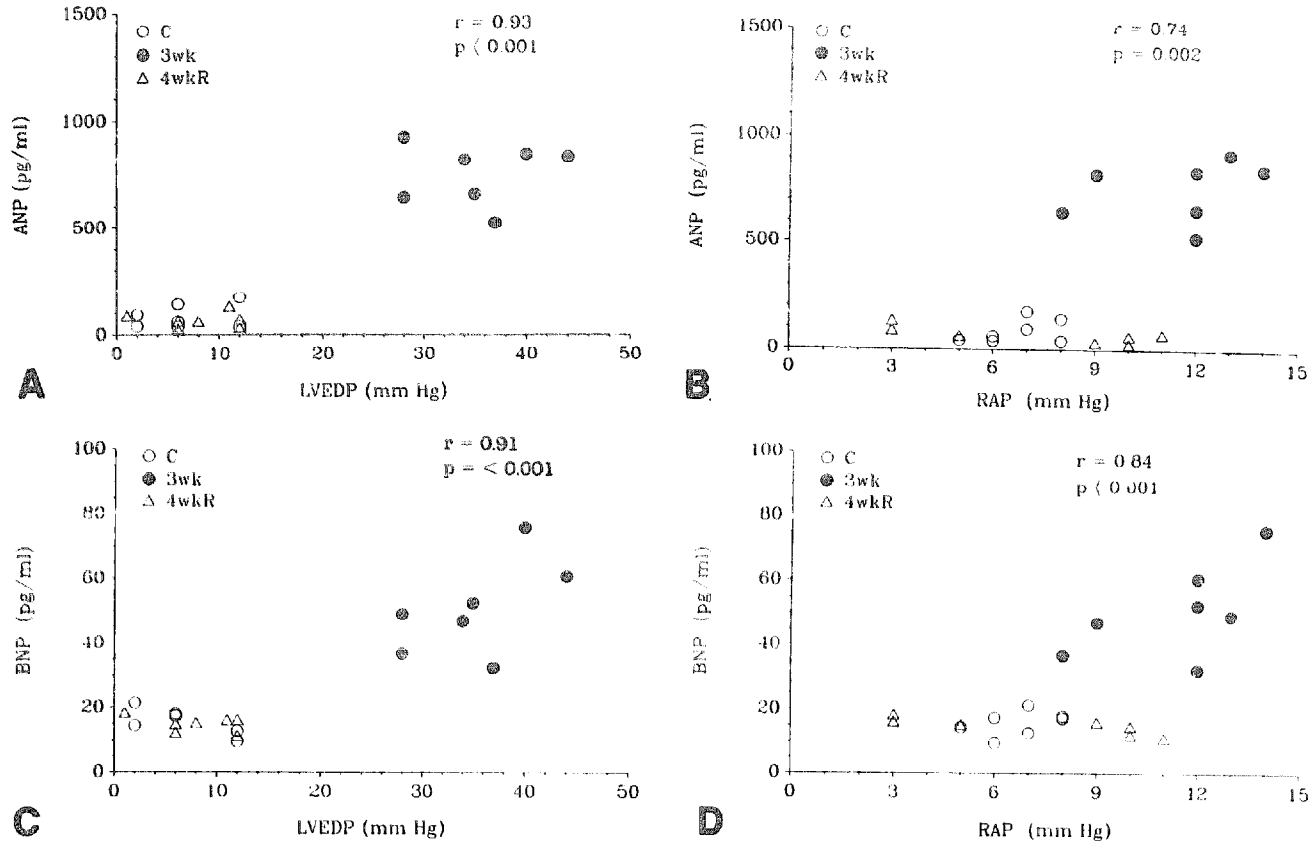


Figure 4. Relation between plasma concentrations of (A) atrial natriuretic peptide (ANP) and left ventricular end-diastolic pressure (LVEDP); (B) atrial natriuretic peptide and right atrial pressure (RAP); (C) brain natriuretic peptide (BNP) and left ventricular end-diastolic pressure, and (D) brain natriuretic peptide and right atrial pressure at control measurement, at 3 weeks of pacing (C, 3wk) and at 4 weeks of recovery after cessation of pacing (4wkR).

tion (8) that plasma renin activity was not significantly increased at 3 weeks of pacing but became markedly elevated with the development of severe heart failure (at 5.1 ± 0.4 weeks of pacing). These observations corroborate our hypothesis (9) that the renin-angiotensin system is not activated until an advanced stage of heart failure in this model.

Plasma atrial and brain natriuretic peptide concentrations. The directionally similar changes of plasma atrial natriuretic peptide and brain natriuretic peptide, as well as their close relation with cardiac filling pressures, indicate that the two peptides act together as a dual natriuretic vasodilator system in the maintenance of circulatory homeostasis in heart failure. Like atrial natriuretic peptide, brain natriuretic peptide is a cardiac hormone (16–21). Also, extensive brain natriuretic peptidelike immunoreactive neurofibers have recently been found in rat myocardium and in the coronary, cerebral and renal arteries (29). However, the mechanism of release of brain natriuretic peptide, unlike that of atrial natriuretic peptide, has not yet been explored in detail. Our current findings of the similar time course of changes of the plasma concentrations of the two peptides and their close correlation with each other strongly suggest that the stimuli for cardiac release of the two peptides may be quite similar, namely, an increase in cardiac filling pressures.

We have previously shown (30) that plasma atrial natriuretic peptide concentration correlated well with pulmonary capillary wedge pressure and right atrial pressure at 1 week of pacing but not at the time of severe heart failure (4.9 ± 1.8 weeks of pacing). We postulated that this reflected an escape phenomenon, possibly related to an attenuated cardiac release of the peptide (30). In the current study, both atrial and brain natriuretic peptide correlated well with left- and right-sided cardiac filling pressures examined over a wide range of such pressures at all study time points. However, as expected, when only the heart failure data (3 weeks of pacing) were analyzed, plasma atrial natriuretic peptide concentrations did not correlate with left ventricular end-diastolic pressure ($r = 0.06$, p = NS) and correlated poorly with pulmonary capillary wedge pressure ($r = 0.45$, $p < 0.05$) and right atrial pressure ($r = 0.32$, p = NS). At 3 weeks, brain natriuretic peptide correlated modestly with left ventricular end-diastolic pressure ($r = 0.56$, $p < 0.05$), did not correlate with pulmonary capillary wedge pressure ($r = -0.22$, p = NS) but correlated with right atrial pressure ($r = 0.61$, $p < 0.05$). This lack of consistent correlation between plasma concentrations of the two peptides and cardiac filling pres-

sures suggests that, although both atrial and brain natriuretic peptides are released in response to increased cardiac filling pressures, the response may be attenuated as heart failure becomes progressively more advanced. Conversely, at heart failure (3 weeks), a correlation between plasma concentrations of atrial and brain natriuretic peptide remained ($r = 0.66$, $p < 0.05$), suggesting that either the two peptides are released together from the heart or that the activation of one peptide influences the activation of the other.

In this study, although the directional changes of the two peptides were similar, there were notable differences. 1) At all times plasma concentration of brain natriuretic peptide was much lower than that of atrial natriuretic peptide. At control conditions, brain natriuretic peptide concentration was approximately one fifth the atrial natriuretic peptide concentration, a ratio similar to that observed in normal humans (22,31) and higher than that observed in pigs (16) and rats (32). These data suggest that plasma brain natriuretic peptide concentration is probably lower than atrial natriuretic concentration in most species.

2) During evolving heart failure, the percent increases from control values are smaller for brain natriuretic peptide than for atrial natriuretic peptide. This smaller increase may partly reflect a lower cardiac tissue concentration of the peptide. In both the porcine and the human heart (17,31) brain natriuretic peptide concentration was shown to be much lower than atrial natriuretic peptide concentration in the atrium and the ventricle. Furthermore, in most species, the concentration of brain natriuretic peptide, like that of atrial natriuretic peptide, is much higher in the atrium than in the ventricle (17,32). Notwithstanding this observation, in the failing human heart the ventricle is thought to be a more important source of production of brain natriuretic peptide than of atrial natriuretic peptide (32). Further studies in other species will be required to confirm this hypothesis.

3) After cessation of pacing, the concentration of plasma brain natriuretic peptide concentration appears to decline more slowly than that of atrial natriuretic. This finding, coupled with the previous observation that the percent increase of brain natriuretic peptide is less than that of atrial natriuretic peptide, suggests that in this dual natriuretic mechanism, brain natriuretic peptide may be less responsive to changes in cardiac filling pressures. Alternatively, it may reflect a slower clearance from the circulation than atrial natriuretic peptide, such as that observed in humans (32). We may therefore speculate that, whereas atrial natriuretic peptide is responsible for modulating sudden changes in hemodynamics, brain natriuretic peptide may serve to modulate longer term changes.

To further understand the function of brain natriuretic peptide and its relation to atrial natriuretic peptide, it is useful to review the current knowledge regarding natriuretic peptide receptors. The A- and B-receptors (ANPR-A and ANPR-B, respectively) are linked to guanylate cyclase and are responsible for the actions of the peptides (33,34). Receptor ANPR-A is activated most efficiently by atrial natriuretic peptide and, to a lesser degree, by brain natriuretic peptide (34). Receptor ANPR-B requires large concentrations of atrial and brain natriuretic peptide to become activated and appears to be specific for the newly described C type natriuretic peptide (33–35). The C-receptors (ANPR-C), in contrast, are the clearance receptors not linked to guanylate cyclase, and these receptors are able to recognize all three peptides (33,35). These observations indicate peptide specificity with regard to their natriuretic peptide receptors.

Given this peptide specificity for ANPR-A and ANPR-B and the observed widespread neurofiber innervation of immunoreactive brain natriuretic peptide in the cardiovascular tree cited earlier (29), it is possible that brain natriuretic peptide serves functions distinct from those of atrial natriuretic peptide, one of which may be neuroregulation of the circulation. Furthermore, one may speculate that increased atrial and brain natriuretic peptide concentrations may compete with each other for C-receptors, resulting in an increased amount of the less avid uncleared peptide. This would provide another explanation for the excellent correlation between plasma atrial and brain natriuretic peptide concentrations observed in our study. Competition between atrial and brain natriuretic peptide for C-receptors has been proposed as an explanation for the observation in humans that infusion of brain natriuretic peptide results in increased plasma atrial natriuretic peptide concentration (34). Finally, it is also possible that the increase in plasma brain natriuretic peptide concentration may be mediated by reduced clearance of the peptide in heart failure.

We and others (38–40) have previously reported blunted natriuretic response to exogenous atrial natriuretic peptide in heart failure. Results of studies on the biologic actions of brain natriuretic peptide in heart failure have been conflicting. In rats with high output cardiac failure, the renal effects of synthetic brain natriuretic peptide are attenuated (41). However, in patients with heart failure (37) and in dogs with pacing-induced heart failure (42), the natriuretic effect of infused brain natriuretic peptide appears to be greater than that in normal control subjects. The significance of these observations remain to be determined.

Certain aspects of the current study warrant further note:

1) In the current study, pacing was maintained for 3 weeks rather than for a variable period dictated by clinical and radiographic evidence of severe heart failure, as used in our previous studies (8,23,24). Hence, these animals had less advanced heart failure than that of animals in our previous studies. Had we paced the dogs to the biologic end point of severe heart failure, as described previously (8,23,24), we would probably have observed a significant increase in plasma renin activity.

2) Because porcine polyclonal antibodies were used to determine brain natriuretic peptide concentration, we cannot exclude the possibility that absolute plasma concentrations

were underestimated. However, such underestimation would not be expected to have a major impact on the time course of changes of plasma brain natriuretic peptide concentration or the relation with cardiac filling pressures and atrial natriuretic peptide concentrations.

Conclusions. The current study documents the activation of a dual natriuretic peptide system during evolving heart failure and the deactivation of this system after recovery from heart failure. The close relation between brain natriuretic peptide concentrations and cardiac filling pressures indicates that this peptide, like atrial natriuretic peptide, is responsive to changes in these pressures. However, there are differences between the two peptides. It is possible that brain natriuretic peptide serves a more specialized function than atrial natriuretic peptide and may be involved in regulation of more chronic hemodyamic changes, such as those found in heart failure. Studies comparing the responses of the two peptide systems with acute changes in cardiac filling pressures under normal conditions and in heart failure, as well as documentation of changes in cardiac tissue brain natriuretic peptide concentrations, may provide further insights into our observations.

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